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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/882,621	06/15/2001	Erwin Houtzager	4957US	8472

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/882,621	HOUTZAGER ET AL.	
	Examiner	Art Unit	
	Gerald G. Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/24/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 1/24/2005, in which several claims were cancelled (claims 1-25 & 46-52) and in which several new claims were added (claims 53-71). Claims 26-45 & 53-71 are pending in the instant application, with claims 26-45 withdrawn from consideration as being directed to nonelected inventions.

Any rejection of record not addressed herein is withdrawn. This action is Final.

Claim Objections

Claim 67 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 53, upon which claim 67 is dependent, already specifies that the fusion protein of part (a) renders the phage to which it is attached infectious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-54 & 58-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. **This rejection is maintained for reasons of record in the previous office action and which are repeated below.**

Each of the rejected claims is directed to a chimeric phage, collections of phage comprising at least one chimeric phage and methods of making a chimeric phage. The chimeric phage of the invention comprises: (i) a fusion protein wherein a proteinaceous molecule is fused to a "functional form" of a phage coat protein, and (ii) a "mutant form" of the same phage coat protein. The "mutant form" is characterized by an inability or reduced ability to mediate infection of a bacterial host in the absence of either the wildtype coat protein or a "functional form" of the coat protein (e.g. a phage comprising no wildtype phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infection than a phage comprising no wildtype copies of the coat protein and having a coat comprising said mutant form and at least one copy of the functional form). The claims are enormously broad genus claims in that they encompass literally *any* type of phage (e.g. filamentous phage, phage having an icosahedral head, phage with or without tail structures, phage having ssDNA, dsDNA or RNA genomes, etc.). Further, the claims are directed to chimeric phage having very specific functional limitations with regard to the specific coat protein that is mutagenized to be inactive in its "mutant form" and to restore infectivity when presented as a "functional form" as part of a fusion polypeptide. Thus, the claims encompass an enormously broad genus of phage and phage coat proteins having very specific functional properties.

The entire disclosure of the specification is directed to the description of particular filamentous phage strains (e.g. M13 or R408) where the g3 protein, which mediates infection of

bacterial host cells, is mutated to yield both a "mutant form" (e.g. g3D3 proteins lacking the D1 & D2 domains of the g3 protein) and "functional forms" (e.g. presumably full-length g3 proteins comprising protein fusions at the amino-terminal end of the g3 protein; e.g. see Figure 1). The presence of the g3D3 domain in addition to the g3/fusion "functional form" allows for the stabilization of phage particles that comprise less than 5 copies of the "functional form" and decreases the "background" of particles that do not comprise a functional form because such particles are non-infectious in this system. No other teachings are provided regarding the specific coat proteins that might be used analogously for other types of bacteriophage (e.g. T4, T7, P2, λ, etc.). For example, there is no description of what would be a "functional form" of any of the coat proteins for any other bacteriophage such that the fusion protein comprising the coat protein restores infectious activity to a phage particle comprising a mutant form of the same protein. Thus, the instant specification does not provide any structural/functional basis for the skilled artisan to envision other, non-filamentous embodiments of the claimed chimeric phage.

While there do appear to be filamentous phage systems that appear to meet the recited limitation for the "mutant form" and "functional form" of the coat protein (i.e. see the rejection under 35 U.S.C. 102(b) over U.S. Patent No. 6,027,930 below), the prior art does not appear to teach other types of chimeric phage (e.g. icosahedral phage such as λ) that would necessarily meet the very specific functional limitations of the claims. In fact, the prior art teaches that assembly of phage particles is an exceedingly complex process. Moody provides a review of phage assembly that describes how different types of phage have tackled the problem of encapsulating the phage genetic material in a protective structure that itself relies on a minimum of genetic information to encode the head structure (Michael F. Moody. Journal of Molecular

Biology 1999, Vol. 293, pages 401-433; see the entire document). Generally speaking this involves using a minimum number of different protein subunits (i.e. requiring less genetic information) to form a complex 3-dimensional structure that can accommodate the genetic material (e.g. an icosahedron in the case of large dsDNA bacteriophage). To do this the major head protein subunits must be able to interact with one another in *equivalent* and *quasi-equivalent* ways that involve several protein-protein interactions for each subunit monomer. For example, the different head structures for different types of phage heads shown in Figure 3 of the Moody reference each show how a single protein monomer (represented by the smaller triangles) can interact with itself to form axes of 5-fold or 6-fold symmetry within the same structure. Thus, at each vertex in the structures shown in Figure 3, each monomer of the major head protein can have a 5-fold or 6-fold interaction with adjacent proteins.

Moody teaches that as the required size of the phage head increases (i.e. to encapsulate a larger viral genome) additional proteins are required to help deal with an increased requirement for quasi-equivalent interactions amongst the subunits in assembly of the head structure. For example, these proteins would include endoscaffolding or exoscaffolding proteins and/or other proteins that can remain as part of the mature phage head (e.g. page 404, last paragraph of column 1 to column 2, second paragraph; page 407, column 1 to page 408, column 2). Moody teaches that assembly of the phage head is a complex process that is liable to errors, resulting in malformed heads such as tubes, spirals or polyhedrons (e.g. page 408, column 2 to page 411, column 1). Moody further teaches that all of the larger dsDNA phage heads undergo some sort of maturation to form a more stable, stronger structure that is more resistant to mechanical or chemical stress and that results in a simultaneous increase in head volume (e.g. page 413, column

2 to page 416, column 1). This process involves modification of at least one of the phage head proteins such as proteolytic cleavage (e.g. T-even phage) or chemical modification (e.g. phage P22, lambda or T7). In the maturation process the protein-protein interactions of the subunits of the phage head are necessarily altered, even resulting in the translocation of subunit domains from the inner to the outer surface of the phage head (e.g. in phage T4) (page 414, columns 1-2). Thus, phage head assembly is a complex process, involving multiple protein-protein interactions that change during the process and involving several different types of proteins. Thus, the prior art provides no basis for the skilled artisan to envision which manipulations of a given coat protein for a given phage will allow the skilled artisan to produce a chimeric phage having the very particular functional properties recited in the rejected claims.

Given the enormous breadth of phage encompassed by the rejected claims, the very specific functional limitations for the recited phage, the complexity of phage morphogenesis and the lack of a structural/functional basis from the instant specification or prior art for the skilled artisan to envision embodiments of the claimed invention other than filamentous phage comprising the g3 protein, the skilled artisan would not have been able to envision a sufficient number of chimeric phage meeting the functional limitations of the claim to describe the broadly claimed genus of such chimeric phage. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the broadly claimed genus of such chimeric phage.

Response to Arguments

Applicant's arguments filed 1/24/2005 have been fully considered but they are not persuasive. The response essentially argues that the amendment of the claims to read only on filamentous phage display systems has obviated the outstanding grounds of rejection.

While the amendment of the claims to limit the scope of the invention to filamentous phage display systems is helpful, it does not fully overcome the grounds of rejection made above. The examiner did not suggest, as is implied in the response, that such a limitation would overcome the outstanding grounds of rejection. As underscored above, there is insufficient basis in the instant specification and prior art to envision embodiments of the specifically recited phage display system that utilize other filamentous phage capsid proteins. Neither the instant specification nor the prior art describe a system where a capsid protein other than gIII is used wherein a first nucleic acid molecule provides a fusion protein comprising a proteinaceous material operatively linked to the wildtype protein (or a part, derivative or analogue thereof) that renders the phage infectious and where a second nucleic acid molecule provides all of the necessary phage functions to for assembly of the filamentous phage particle in the host cell as well as a mutated form of the capsid protein. It would be remedial to amend the claims to recite that the chimeric phage is a filamentous phage and that the capsid protein is the g3 protein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 66, 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 is vague and indefinite in that it is unclear as to what members in the recited group of binding molecules are encompassed by the limitation "a functional part thereof".

Claim 70 is vague and indefinite in that it is unclear the nature and number of steps required for one to obtain a "derivative" of the recited phage strains. For example, how much of the resulting chimeric phage must be "derived from" the recited strain in order for it to satisfy the claim limitation?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 53-68 & 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Rudert et al (FEBS Letters, 1998, Vol. 440, pages 135-140; see the entire reference). **This is a new rejection based on the art supplied in applicants' IDS submitted on 1/24/2005.**

Rudert et al teach a filamentous phage-based system to select multiple protein-protein interactions simultaneously from combinatorial libraries (e.g. Abstract). The system taught by Rudert et al is a modification of the Selectively Infective Phage approach where the modification comprises co-packaging of phage and phagemid vectors into the same hetero-polyphage (e.g.

Figure 2). Like similar SIP systems, Rudert et al utilize a nucleic acid encoding a gIII C-terminal fusion to display a ligand from a protein/protein binding pair as well as a nucleic acid encoding a gIII-N1-N2 fusion comprising the cognate binding partner. Interaction of the gIII C-terminal fusion with the gIII N1-N2 fusion via interaction of the binding pair restores infectivity of the filamentous phage (e.g. Figures 1 & 2). In this system, the gIII C-terminal fusion is the mutant capsid protein recited in part (b) of claim 53. The gIII N1-N2 fusion is the fusion protein of part (a) as recited in claim 53. As shown in Figure 2, both proteins are encoded by nucleic acid sequences under the operative control of regulatable Lac promoters (e.g. Figure 2A-B) and both are packaged into the chimeric phage (Figure 2C). Rudert et al teach that it was necessary to develop phage and phagemid constructs that comprise interference resistant (IR) origins of replication (e.g. Figures 2A-B; Section 3.2 on page 136).

With regard to the recitation in claim 60 of a "functional equivalent" of an AraC/BAD promoter, concept of what is a "functional equivalent" of an AraC/BAD promoter is not explicitly defined in the specification. Therefore, the Lac operator/promoter elements taught by Rudert et al meets this limitation in that it is a regulatable promoter (e.g. addition of IPTG to the culture). With regard the recitation in claim 63 that the first and second nucleic acids comprise codons that do not lead to homologous recombination between the two nucleic acids, one of skill in the art would recognize that there are numerous codons present in the unique regions of the two different vectors that would not be expected to mediate homologous recombination between the two vectors (e.g. the different antibiotic resistance markers). The recitation of a "functional part thereof" in claim 66 can be interpreted to encompass any amino acid sequence found in any of the recited molecules that is also present in the exemplified embodiment taught by Rudert et al

(i.e. in pep3 and p75 ICD domains). The phage fIR3 comprises an IR domain obtained from R408 and is thus "derived from" the R408 strain. In addition, the nature and number of steps required in order to obtain a "derivative" of the recited strains is not explicitly defined in the instant specification. Therefore, any chimeric phage taught in the prior art can be reasonably considered as being a "derivative" of the recited strains. Thus, claim 70 is also anticipated.

Conclusion

No claims are allowed.

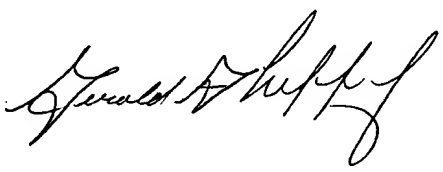
Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 1/24/24 prompted new ground(s) of rejection presented in this Office action. Applicant's amendment necessitated further new ground(s) of rejection presented in this Office action. See MPEP § 706.07(a). See MPEP § 609(B)(2)(i). Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G. Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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